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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Warrell et al.

Application No.: 09/709,170

Group Art Unit: To be assigned

Filed: November 10, 2000

Examiner: To be assigned

For: METHODS OF TREATMENT OF A  
BCL-2 DISORDER USING BCL-2  
ANTISENSE OLIGOMERS

Attorney Docket No.: 10412-025

**INFORMATION DISCLOSURE STATEMENT  
UNDER 37 C.F.R. §1.56 AND §1.97**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent and Trademark Office of all references known by Applicants or their attorneys to be material to patentability of the claimed invention, Attorneys for Applicant hereby direct the Examiner's attention to references AA through CV which are listed on the accompanying Revised Form PTO-1449. Legible copies of references AA-CV are submitted herewith.

Identification of the above-listed references is not to be construed as an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the instant application. Consequently, Applicant respectfully declines to use Form PTO-1449 since that form identifies all references cited therein as "Prior Art." As an alternative, Applicant submits herewith a "Revised Form PTO-1449" entitled "List of References Cited."

Applicant respectfully requests that the Examiner review each of the references identified on the attached Revised Form PTO-1449, and that the references be made of record in the file history of the above-captioned application.

Pursuant to 37 C.F.R. § 1.97(b)(3), since this Information Disclosure Statement is being submitted before the mailing date of a first Office Action on the merits in connection with the instant application, no fee is believed to be due. However, should the Patent and

Trademark Office determine that a fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A duplicate of this document is enclosed for accounting purposes.

Respectfully submitted,

February 23, 2001

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Enclosure

**LIST OF REFERENCES CITED BY APPLICANT**

(Use several sheets if necessary)

ATTY. DOCKET NO.

10412-025

APPLICATION NO.

09/709,170

APPLICANT

Warrell et al.

FILING DATE

November 10, 2000

GROUP

To Be Assigned

**U.S. PATENT DOCUMENTS**

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,098,890	3/24/92	Gewirtz et al.			
	AB	5,202,429	4/13/93	Tsujimoto et al.			
	AC	5,459,251	10/17/95	Tsujimoto et al.			
	AD	5,734,033	03/31/98	Reed; J			
	AE	5,831,066	06/05/95	Reed; J.			
	AF	6,040,181	03/21/00	Reed; J.			

**FOREIGN PATENT DOCUMENTS**

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AG	88302617	3/24/88	EU				
	AH	WO 94/27426	12/08/94	PCT				
	AI	WO 93/20200	10/14/93	PCT				
	AJ	WO 91/04014	04/04/91	PCT				

**OTHER REFERENCES** (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK	Asseline et al, Nucleic acid-binding molecules with high affinity and base sequence specificity: intercalating agents covalently linked to oligodeoxynucleotides. Proc Natl Acad Sci 1984, Jun;81(11):3297-301
	AL	Bishop JM. The molecular genetics of cancer. Science. 1987 Jan 16;235(4786):305-11.
	AM	Blake et al, Inhibition of rabbit globin mRNA translation by sequence-specific oligodeoxyribonucleotides. Biochemistry. 1985 Oct 22;24(22):6132-8
	AN	Boutorin et al., Synthesis of alkylating oligonucleotide derivatives containing cholesterol or phenazinium residues at their 3'-terminus and their interaction with DNA within mammalian cells. FEBS Lett. 1989 Aug 28;254(1-2):129-32
	AO	Bronner et al., Bcl-2 protooncogene and the gastrointestinal mucosal epithelial tumor progression model as related to proposed morphologic and molecular sequences. Lab. Invest. 1993, 68:43A
	AP	Brooks et al., Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science. 1994 April 22;264(5158):569-71.
	AQ	Buchwald et al., Long-term, continuous intravenous heparin administration by an implantable infusion pump in ambulatory patients with recurrent venous thrombosis. Surgery. 1980 Oct;88(4):507-16
	AR	Campos et al., "High expression of bcl-2 protein in acute myeloid leukemia is associated with poor response to chemotherapy." Blood 1993, 81:3091-6
	AS	Cancer: Principles & Practice of Oncology, DeVita, Jr., Hellman and Rosenberg (eds.) 2 <sup>nd</sup> edition, Philadelphia, PA :J.B. Lippincott Co., 1985
	AT	Cao, Endogenous angiogenesis inhibitors: angiostatin, endostatin, and other proteolytic fragments. Prog Mol Subcell Biol. 1998, 20:161-76

FEB 23 2001

AU	Chapman et al., Phase III multicenter randomized trial of the Dartmouth reimen versus dacarbazine in patients with metastatic melanoma. J. Clin. Oncol. 1999, 17(9):2745-51
AV	Chen et al., Determination of N(G),N(G)-dimethylarginine in human plasma by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl. 1997, May 9; 692(2):467-71
AW	Chi-Hong et al., Nuclease activity of 1,10-phenanthroline-copper: sequence-specific targeting. Proc Natl Acad Sci 1986, Oct;83(19):7147-51
AX	Chu et al., Nonenzymatic sequence-specific cleavage of single-stranded DNA. Proc Natl Acad Sci. 1985, Feb;82(4):963-7
AY	<i>Controlled Drug Bioavailability, Drug Product Design and Performance</i> , Smolen and Ball (eds.), Wiley: New York (1984)
AZ	Cotter et al., Antisense oligonucleotides suppress B-cell lymphoma growth in a SCID-hu mouse model. Oncogene. 1994, Oct;9(10):3049-55
BA	Croce et al., Molecular basis of human B and T cell neoplasia. <i>Advance in Viral Oncology</i> , G. Klein(ed.), New York, Raven Press. 1987, 7:35-51
BB	Crowley et al., Prevention of metastasis by inhibition of the urokinase receptor. Proc Natl Acad Sci 1993, Jun 1;90(11):5021-5
BC	Egholm et al., 1992, <i>Peptide Nucleic Acids (PNA)-Oligonucleotide Analogues With An Achiral Peptide Backbone</i> . J. Am. Chem. Soc 1992, 114:1895-97
BD	Goodchild, Conjugates of oligonucleotides and modified oligonucleotides: a review of their synthesis and properties, Bioconjug. Chem. 1990, 1(3):165-87
BE	Goodson, 1984, "Dental Applications" in <i>Medical Applications of Controlled Release</i> , vol. 2, pp. 115-138
BF	Grover et al., Bcl-2 expression in malignant melanoma and its prognostic significance Eur. J. Surg. Oncol. 1996, 22(4):347-9
BG	Haldar et al., The bcl-2 gene encodes a novel G protein. Nature. 1989 Nov 9;342(6246):195-8
BH	Holt, et al., An oligomer complementary to c-myc mRNA inhibits proliferation of HL-60 promyelocytic cells and induces differentiation. Mol Cell Biol. 1988 Feb;8(2):963-73
BI	Jansen et al., "Bcl-2 antisense therapy chemosensitizes human melanoma in SCID mice" Nat. Med. 1998, 4(2):232-4
BJ	Kitada et al., Reversal of chemoresistance of lymphoma cells by antisense-mediated reduction of bcl-2 gene expression. Antisense Res Dev. 1994 Summer;4(2):71-9
BK	Kitada et al., Investigations of antisense oligonucleotides targeted against bcl-2 RNAs. Antisense Res Dev. 1993 Summer;3(2):157-69
BL	Knorre et al., Reactive oligonucleotide derivatives and sequence-specific modification of nucleic acids. Biochimie. 1985 Jul-Aug;67(7-8):785-9
BM	Langer and Peppas, 1981 "Present and Future Applications of Biomaterials in Controlled Drug Delivery Systems", J. Biomaterials 2(3):201-14
BN	Langer, New methods of drug delivery. Science. 1990 Sep 28;249(4976):1527-33
BO	Lu et al., "Bcl-2 protooncogene expression in Epstein Barr Virus-associated nasopharyngeal carcinoma." Int. J. Cancer 1993, 53:29-35
BP	McDonnell et al., Expression of the protooncogene bcl-2 and its association with emergence of androgen-independent prostate cancer. Cancer Res. 1992, 52:6940-4

	BQ	Min et al., Urokinase receptor antagonists inhibit angiogenesis and primary tumor growth in syngeneic mice. Cancer Res. 1996 May 15;56(10):2428-33
	BR	Miyashita et al., bcl-2 gene transfer increases relative resistance of S49.1 and WEHI7.2 lymphoid cells to cell death and DNA fragmentation induced by glucocorticoids and multiple chemotherapeutic drugs. Cancer Res. 1992 Oct 1;52(19):5407-11
	BS	Miyashita et al., Bcl-2 oncoprotein blocks chemotherapy-induced apoptosis in a human leukemia cell line. Blood. 1993 Jan 1;81(1):151-7
	BT	Monia et al., Evaluation of 2'-modified oligonucleotides containing 2' deoxy gaps as antisense inhibitors of gene expression, J. Biol. Chem. 1993, 268:14514-22
	BU	Morvan et al., alpha-DNA. I. Synthesis, characterization by high field 1H-NMR, and base-pairing properties of the unnatural hexadeoxyribonucleotide alpha-[d(CpCpTpTpCpC)] with its complement beta-[d(GpGpApApGpG)]. Nucleic Acids Res. 1986 Jun 25;14(12):5019-35
	BV	Negrini et al., Molecular analysis of mbcl-2: structure and expression of the murine gene homologous to the human gene involved in follicular lymphoma. Cell. 1987 May 22;49(4):455-63
	BW	Paoletti C. Anti-sense oligonucleotides as potential antitumour agents: prospective views and preliminary results. Anticancer Drug Des. 1988 Mar;2(4):325-31
	BX	<i>Physicians' Desk Reference</i> , 54 <sup>th</sup> Edition (2000)
	BY	Raynaud et al., Pharmacokinetics of G3139, a phosphorothioate oligodeoxynucleotide antisense to bcl-2, after intravenous administration or continuous subcutaneous infusion to mice. J Pharmacol Exp Ther. 1997 Apr;281(1):420-7
	BZ	Reed, Regulation of apoptosis by bcl-2 family proteins and its role in cancer and chemoresistance Curr. Opin. Oncol. 1995, 7:541-6
	CA	Reed et al., Regulation of chemoresistance by the bcl-2 oncoprotein in non-Hodgkin's lymphoma and lymphocytic leukemia cell lines. Ann Oncol. 1994;5 Suppl 1:61-5
	CB	Reed et al., Antisense-mediated inhibition of BCL2 protooncogene expression and leukemic cell growth and survival: comparisons of phosphodiester and phosphorothioate oligodeoxynucleotides. Cancer Res. 1990 Oct 15;50(20):6565-70
	CC	Reed et al., "Differential expression of bcl-2 protooncogene in neuroblastoma and other human tumor cell lines of neural origin." Cancer Res. 1991 51:6529-38
	CD	Reed et al., BCL2-mediated tumorigenicity of a human T-lymphoid cell line: synergy with MYC and inhibition by BCL2 antisense. Proc Natl Acad Sci 1990 May;87(10):3660-4
	CE	Reed et al., Regulation of bcl-2 proto-oncogene expression during normal human lymphocyte proliferation. Science. 1987 Jun 5;236(4806):1295-9
	CF	Selzer et al., Expression of Bcl-2 family members in human melanocytes, in melanoma metastases and in melanoma cell lines. Melanoma Res. 1998 Jun;8(3):197-203
	CG	Stein et al., Oligodeoxynucleotides as inhibitors of gene expression: a review. Cancer Res. 1988 May 15;48(10):2659-68.
	CH	Stein et al., Physicochemical properties of phosphorothioate oligodeoxynucleotides. Nucleic Acids Res. 1988 Apr 25;16(8):3209-21
	CI	Strasser et al., bcl-2 transgene inhibits T cell death and perturbs thymic self-censorship. Cell. 1991 Nov 29;67(5):889-99

FEB 23 2001

	CJ	Stull et al., Antigen, ribozyme and aptamer nucleic acid drugs: progress and prospects. Pharm Res. 1995 Apr;12(4):465-83
	CK	Treat et al., 1989, "Liposome Encapsulated Doxorubicin Preliminary Results of Phase I and Phase II Trials" in <i>Liposomes in the Therapy of Infectious Disease and Cancer</i> , Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-65
	CL	Tsujimoto et al., Involvement of the bcl-2 gene in human follicular lymphoma. Science 1985, 228:1440-1443
	CM	Uhlmann et al., EMD 53998 acts as Ca(2+)-sensitizer and phosphodiesterase III-inhibitor in human myocardium. Basic Res Cardiol. 1995 Sep-Oct;90(5):365-71
	CN	Vlassov et al., Complementary addressed modification and cleavage of a single stranded DNA fragment with alkylating oligonucleotide derivatives. Nucleic Acids Res. 1986 May 27;14(10):4065-76
	CO	Waters et al., Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. J Clin Oncol. 2000 May;18(9):1812-23
	CP	Webb et al., BCL-2 antisense therapy in patients with non-Hodgkin lymphoma. Lancet. 1997 Apr 19;349(9059):1137-41
	CQ	Webb et al., Hybridization triggered cross-linking of deoxyoligonucleotides. Nucleic Acids Res. 1986 Oct 10;14(19):7661-74
	CR	Wickstrom et al., Human promyelocytic leukemia HL-60 cell proliferation and c-myc protein expression are inhibited by an antisense pentadecadeoxynucleotide targeted against c-myc mRNA. Proc Natl Acad Sci 1988 Feb;85(4):1028-32
	CS	Williams, Programmed cell death: apoptosis and oncogenesis. Cell. 1991 Jun 28;65(7):1097-8
	CT	Yunis et al., Bcl-2 and other genomic alterations in the prognosis of large-cell lymphomas. N. Engl. J. Med. 1989, 320:1047-54
	CU	Zamecnik et al., Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA. Proc Natl Acad Sci 1986 Jun;83(12):4143-6
	CV	Zamecnik and Stephenson, Inhibition of Rous sarcoma virus replication and cell transformation by a specific oligodeoxynucleotide. Proc Natl Acad Sci 1978 Jan;75(1):280-4
EXAMINER		DATE CONSIDERED

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.